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MALARIA.

INTEREST in malaria has been very greatly increased as a result of three factors due to the present war: (*a*) large numbers of non-immune service men have had to fight in areas where malaria is prevalent, and many of them have contracted the disease; (*b*) Java, which, prior to the war, produced about 90% of the world's supply of quinine, has been taken by the Japanese; and (*c*) these immediate problems have combined to produce the possibility of a third, namely, that convalescent patients returning to parts of Australia where *Anopheles* is already prevalent will provide a reservoir of gametocytes from which the disease may spread to the mosquitoes, and so to the civil population. It is by no means certain that such transmission will occur on a significant scale; but the situation does appear to be similar, in some respects, to that in Britain during the last war, when soldiers convalescing from malaria were often sent to Kent and Essex, and the *Anopheles* present in certain parts of these counties disseminated the disease amongst healthy soldiers and civilians.

The importance of malaria in warfare has, of course, long been recognized. It was a decisive factor in the campaigns staged in Iraq, Salonika, East Africa and Palestine during the war of 1914 to 1918, and had been just as important in some phases of previous wars. Moreover, malaria has remained a scourge in certain countries during times of peace; for example, one-half of the three hundred and fifty million inhabitants of India suffer from the disease, and every year one million of them die from it.

It is therefore probably true to say that when war broke out, and especially when it threatened to spread to the Pacific, the medical services fully realized the magnitude of the problem of malaria. Many lectures and refresher courses on this topic have been given to doctors during the last few years, and a great deal of literature on the subject has been circulated. The following account is presented in an attempt to summarize some of the more important and more recent literature for those who have not had the opportunity of consulting these original documents.

Distribution of Malaria in the Pacific.

Malaria is endemic in certain parts of Australia: the north-west of Western Australia; the more northern parts of Northern Territory; and the north and north-east of Queensland. The places in Australia in which malaria has occurred during this century are shown in detail on a map in Cilento's book, "Tropical Diseases in Australasia".[1] There is, of course, no finality about this list; for example, a patient has already contracted malaria at Bega, on the south coast of New South Wales, 37° south of the equator.[2] The endemic season in Australia begins with the end of the heavy rains in April, and lasts until September. It is determined by that period during which pools of water are available for mosquito breeding, while at the same time there are no heavy rains to wash the eggs out to sea.

As far as the Pacific Islands are concerned, the disease has not occurred east of meridian 170°, and, apart from the single case just quoted, has not been encountered south of about parallel 34°; further, it probably does not occur in places more than 4,000 feet above sea-level.[3] This generalization may be amplified by the following statements. (i) The following Pacific areas are subject to malaria: Papua, including Trobriand Islands; New Guinea; the Mandated Territory of New Guinea, including the Bismarck Archipelago; the Solomon Islands; the Santa Cruz Islands; and New Hebrides. In these regions there are certain places such as Port Moresby, Samarai Islands, and Rabaul which are kept free of malaria, but the price of this freedom is eternal vigilance, because there are heavily infested areas close by, for example, the Milne Bay area near Samarai. In New Guinea the periods of hyperendemicity occur during the wet season from December to June, at which period there are innumerable pools of water and other climatic conditions are suitable for the breeding of mosquitoes. (ii) The following areas are free of malaria: New Caledonia; Loyalty Islands; Fiji Islands; Tonga Islands; the Hawaiian Islands; and the Japanese-held territory of Ellice Islands and Gilbert Islands. Of course, neither of these lists is comprehensive.

It will be noticed that amongst the malaria-free areas are certain places of strategic importance, such as New Caledonia, which is on the supply route between the United States and Australia, and the Hawaiian Islands, which are the main American bulwark in the Pacific. Fear has been expressed that malaria may spread to these and other islands; there is a precedent for such an occurrence in that an introduced *Anopheles* carried from Africa by aeroplane or fast destroyer was believed to be responsible for an extensive and severe outbreak of malaria in Brazil in 1931.[4] Taylor has, however, expressed the following opinion in regard to the possibility of the introduction of *Anopheles* into those Pacific Islands now free of it:[5]

> This [that is, the spread of Anopheles to the islands east of 170° meridian] seems somewhat doubtful, because there has been ample opportunity for such introduction to have taken place in the past by means of inter-island lugger and small steamship travel. It may still be possible for it to take place today by means of the aeroplane, but if the fighting forces exercise the care they should, even for their own sakes, and spray out machines arriving back at their bases, then there should be but a very limited risk of the introduction of any insect pests into a new area. . . . Supposing some Anophelines did elude the vigilance of the Air Force hygiene staff. . . . I do not think Anophelines or other mosquitoes would obtain a foothold in "American Polynesia", since the fish *Gambusia affinis* has long been established on many of the islands in the Central Pacific.

The Mosquito Vector of Malaria.

It is well known that the mosquitoes that transmit malaria belong to the genus *Anopheles*, which has the following readily recognized characteristics: the wings are usually spotted, but not in all cases; the resting attitude is one in which the body is tilted downward at the head end; the palps of the female are as long, or almost as long, as the proboscis; the eggs are laid singly, or in star-shaped clusters, and each possesses a float; the larvæ lie parallel to the surface of the water and immediately below it. The identification of the various species of *Anopheles*, however, should be carried out only by a trained entomologist. Such work is extremely important in the investigation of a local outbreak of malaria. Many species which can be infected experimentally with the disease are not necessarily infected under natural conditions, and the same variety

may differ from time to time and from place to place in its effectiveness as a vector. Unless the mosquitoes actually carrying the malaria parasite are found and identified, time and money may be wasted on anti-mosquito measures which have little or no effect on the incidence of the disease. There are 150 or more recognized species of *Anopheles*, some 70 of which have been incriminated as potential vectors of malaria.

An investigation was carried out at Cairns last year to determine the mosquitoes that were playing a part in a local epidemic. It was found that *Anopheles punctulatus*, variety *moluccensis*, was widespread in houses and was undoubtedly the vector. For the first time in Australia actual sporozoites were seen in the salivary glands of some specimens captured in homes. In the past, *Anopheles bancrofti* and *Anopheles annulipes*, variety *mastersi*, have been considered likely vectors; in Cairns the former was commonly discovered in breeding places, but did not frequent the houses so much, and was not found infected; the latter was not caught in houses at all and was also not found infected. Infection was demonstrated in one specimen of *Anopheles amictus*. These results, like similar findings elsewhere, can be regarded as necessarily true only in reference to one particular occasion at one particular town. *Anopheles punctulatus*, variety *moluccensis*, has been incriminated on one previous occasion, when it and *Anopheles punctulatus* were shown to be vectors in New Britain in 1923.[1] It has been found in Townsville, Cairns, Charters Towers, Mount Isa, Mareeba, Atherton, and from Darwin to Katherine.[2]

Life Cycle of the Malarial Parasite.

The malarial parasite undergoes two cycles—an asexual which takes place in man, and a sexual which is passed in the mosquito; and an understanding of this life history is essential in the rational therapy of malaria.

The asexual cycle begins with the inoculation of sporozoites by the bite of a mosquito. The stage of development immediately succeeding this is not known: the parasites cannot be detected either by examination of the blood, or by inoculation of large quantities of it into a susceptible subject; they are, moreover, insusceptible to all known anti-malarial drugs. It is possible that they may be undergoing an extra-erythrocytic cycle within the endothelial cells, for this is known to occur in the case of some plasmodia that infect birds.

After a few days the parasites appear in the red blood cells and each develops a vacuole which pushes the nucleus to one side and gives rise to the "signet-ring" form. This increases in size and becomes irregular, while brownish granules of altered blood pigment appear in its cytoplasm. This stage is known as the trophozoite. When the trophozoite reaches maturity the pigment collects into a central block and the cytoplasm and chromatin become arranged around the periphery to form a number of spore-like bodies. The parasite is then known as a schizont: it soon ruptures the red blood cell, and the spore-like bodies are liberated into the blood stream under the name of merozoites. These penetrate further red cells and the asexual cycle begins again. The time taken for the schizogony cycle varies with the four species of malarial parasite: *Plasmodium vivax* takes 48 hours; *Plasmodium falciparum*, 24 to 48 hours; *Plasmodium malariæ*, 72 hours; and *Plasmodium ovale*, 48 hours. There is a temperature cycle in the patient corresponding in duration to the schizogony cycle in the parasite, and there are therefore the following types of malarial fever: benign tertian due to *Plasmodium vivax*, malignant tertian or subtertian due to *Plasmodium falciparum*, quartan due to *Plasmodium malariæ*, and a tertian type due to *Plasmodium ovale*.

The gametocytes which form the starting point of the sexual cycle are derived directly from merozoites. In benign tertian malaria they occur early and are commonly seen when the blood of a patient who has just developed a primary infection is examined. In malignant tertian malaria, however, there is a delay of about ten days between the peak of the trophozoite count and the peak of the gametocyte count. Gametocytes live for about ten days, on the average, and cannot complete their development except in the mosquito. In the stomach of this insect they change into gametes and fertilization takes place. The resulting ookinete penetrates to the outer aspect of the stomach wall and forms an oocyst which becomes packed with sporozoites. When the oocyst ruptures, the sporozoites are liberated into the body cavity of the mosquito. Some of them enter the salivary glands and are conveyed to the person whom the mosquito next bites. The mosquito is infective on about the tenth day after it first ingested blood containing gametocytes, and, for practical purposes, may be considered to remain infective for the rest of its life.

Natural History of Untreated Malaria.

The natural history of untreated malaria has four phases: (*a*) the incubation period; (*b*) the primary period of symptoms; (*c*) the latent period; and (*d*) the period of recrudescence and relapse.

The incubation period usually lasts about a week to ten days in malignant tertian infections, a little longer in benign tertian, and up to six weeks in quartan malaria. Consequently, when mixed infections occur it is frequently only the malignant tertian which is diagnosed at the first attack.

The primary period of symptoms often begins in a manner not usually considered typical of a malarial fever. Later, however, the characteristic regularity of the attacks of fever and its accompanying symptoms generally become manifest. It is not intended to review the symptoms and signs of malaria, but the chief phenomena associated with a primary attack may be classified as: fever; anæmia; jaundice; accumulation of pigment in the tissues; toxic changes in organs, especially the liver; blocking of capillaries, especially of the brain, heart, gastro-intestinal tract and skin; and changes associated with the development of immunity. The clinical picture resulting from these effects is often characteristic, but the diagnosis of malaria should always be supported by the demonstration of parasites in the blood; otherwise such important differential diagnoses as that between malaria and heat hyperpyrexia will not be made.

The immunity reaction that occurs determines the further course of the disease. The immunity is partly cellular, as is shown by the increase in the macrophages of the reticulo-endothelial system—an increase which is reflected in enlargement of the spleen. There is evidence also that humoral immunity plays a part:[3] it has been found possible to demonstrate the existence of circulating antibodies.

The immunity is usually sufficient in malignant tertian, and almost invariably sufficient in other types of malaria, to prevent the death of the patient. The attack comes to an end and there occurs a latent phase which may be interrupted from time to time by a recrudescence of the disease if the immunity of the patient falls below an adequate level.

The Possibility of Epidemics of Malaria in Southern Australia.

There are many factors concerned in the spread of malaria, and they interact with one another in a complex way. The possibility of an epidemic in the southern parts of Australia is therefore difficult to assess, even though we know that some species of *Anopheles* are present and an increased number of gametocyte carriers is to be expected; the scientific attitude to this problem is one of agnosticism.

At the risk of undue simplification, it may be stated that the spread of malaria depends on the presence of (*a*) gametocyte carriers, (*b*) suitable mosquitoes and (*c*) a susceptible population. An infected person is not efficient as a carrier unless he has at least ten gametocytes per cubic centimetre of blood. The number present is decreased by immunity or suppressive treatment, and is increased by lack of immunity, and by a partial but inefficient suppressive treatment. Apparently, too, mere numbers are not sufficient: the gametocytes must be "ripe" before they will readily infect mosquitoes.

Only anopheline mosquitoes are able to transmit malaria, but, as mentioned previously, they do not all transmit it equally well, and the same species of *Anopheles* may be a more dangerous vector at some times than at others. The habits of the mosquito are obviously important in this connexion; the insects may prefer the blood of cattle to that of humans, and they may or may not enter houses readily; these are only two of many habits that may be all-important in the spread of the disease.

Treatment.

Routine Treatment in Cases of Average Severity.

The patient should remain in bed until his temperature has been normal for two consecutive days. He may then be allowed up if his general condition is satisfactory to the clinician. It is usually considered important to prevent constipation and to see that the reaction of the urine remains alkaline. Symptomatic treatment is required: hot drinks and means of warmth during the cold stage; cold drinks, sponging and aspirin during the hot stage; change of pyjamas and bedclothes, and the administration of fluid during the sweating stage.

The standard routine of specific treatment, as recommended by Australian Army authorities, consists of four courses, which follow in order one after the other, the intensive treatment lasting thirteen days, and the maintenance course six weeks: (*a*) ten grains of quinine sulphate are given three times a day for three days; (*b*) 0·1 gramme of "Atebrin" is given three times a day for five days; (*c*) 0·01 gramme of "Plasmoquine" and 5 grains of quinine sulphate are given three times a day for five days; (*d*) 0·1 gramme of "Atebrin" is given on six days each week for six weeks.

It is important that the quinine should be in solution and the following prescription is therefore advised:

Quinine sulphate	10 grains
Dilute sulphuric acid	10 minims
Simple syrup	1 drachm
Chloroform water	to ½ fluid ounce

The sulphuric acid renders the quinine sulphate soluble. The same result can be achieved by using quinine bisulphate directly, but the equivalent dose of this is 25% higher, for example, 12·5 grains of bisulphate as compared with 10 grains of sulphate. The quinine must be given in solution even if the drug is supplied in the form of tablets.

"Atebrin" is liable to cause irritation of the gastro-intestinal tract and is therefore given after meals in a copious draught of water. "Plasmoquine" is administered in a similar way in order to prevent sudden absorption, for the margin of safety between therapeutic and toxic doses is small. The dosage of this drug must be carefully supervised: pamoquin, of the British Pharmacopœia, is "Plasmoquine naphthoate" and only one-half of its weight consists of the active base. The dose of this and similar preparations, therefore, is 0·02 gramme, unless the tablets are expressly labelled in terms of the "Plasmoquine" equivalent.

The plan behind this type of course is supported by both theoretical reasoning and empirical findings. Quinine is given first because it acts more quickly than its substitute "Atebrin", but, in order to conserve the small quantities of quinine available, a change to the substitute drug is made after three days. There is little to choose between "Atebrin" and quinine as far as controlling fever is concerned; they both act on the schizonts of *Plasmodium falciparum*, *Plasmodium vivax* and *Plasmodium malariæ*. There have been instances in which one drug has appeared to be better than the other, but the sum total of experience does not favour the one significantly more than its competitor, and the question of supply becomes a dominant consideration. One factor tentatively advanced in favour of "Atebrin" is the smaller incidence of blackwater fever following its use; if this proves to be true it will reinforce the advantage which "Atebrin" has by being more readily available. The course of quinine and "Plasmoquine" is designed to prevent relapses, and, by destroying gametocytes, to prevent the spread of the disease to mosquitoes. Although quinine and "Atebrin" have essentially the same actions on the malarial parasites, it is essential to use quinine and not "Atebrin" in combination with "Plasmoquine", because "Atebrin" and "Plasmoquine" accentuate the toxic actions of each other, and must never be given concurrently. "Plasmoquine" and quinine are to some extent complementary in their actions: "Plasmoquine" is a very effective gametocide and acts on the sexual forms of all malarial parasites, including the crescents of *Plasmodium falciparum*, which are resistant to quinine; quinine, on the other hand, is a universal schizonticide, whereas "Plasmoquine" is ineffective against the asexual forms of *Plasmodium falciparum*. "Plasmoquine" exerts a very beneficial effect on the relapse rate in malaria, especially benign tertian malaria, and may possibly have an action on the form of parasite which persists between pyrexial attacks.

By way of summary, the actions of the three anti-malarial drugs may be given as follows: (i) Quinine acts on an asexual form (probably schizonts and merozoites) of all three varieties, and on the gametocytes of *Plasmodium vivax* and *Plasmodium malariæ*, but not *Plasmodium falciparum*. (ii) "Atebrin" has essentially the same actions. (iii) "Plasmoquine" acts on an asexual form of *Plasmodium vivax* and of *Plasmodium malariæ*, but not of *Plasmodium falciparum*; it is effective against the gametocytes of all three forms.

The toxic effects of these three drugs are important. Quinine has four main undesirable actions: (*a*) on the special senses, commonly causing transient slight deafness, buzzing or ringing in the ears, and slight giddiness; in larger doses it causes complete deafness, and interference with vision or even quinine amblyopia; (*b*) on blood vessels, causing hæmoglobinuria, epistaxis and hæmorrhages of the skin; (*c*) on the gastro-intestinal tract, causing anorexia, nausea and vomiting; (*d*) on the body tissues generally, causing a hypersensitivity reaction of which the chief features are urticaria, hæmorrhages, vomiting, œdema and collapse. "Atebrin" has two chief toxic effects: (*a*) it may produce gastro-intestinal irritation leading to anorexia, nausea, vomiting and abdominal pain; (*b*) it may cause headache and mental instability, varying from restlessness and excitement to a temporary maniacal psychosis. It frequently causes a slight yellow discoloration of the skin, but this does not involve the conjunctivæ and is not associated with damage to the liver. "Plasmoquine" causes epigastric pain of a dull, aching character; it also acts on red blood cells, sometimes causing oxidation of the hæmoglobin to methæmoglobin, and these effects are revealed in the form of cyanosis in mild cases, and hæmolytic jaundice and hæmoglobinuria in more severe types; acute yellow atrophy may also occur.

Excellent results are obtained by the above and similar types of treatment. Malignant tertian malaria is cured in the vast majority of cases by a single course of therapy. In benign tertian there is a relapse rate which varies with time and place, but so far has usually been 13% or more.

In the standard course quinine has been replaced as far as possible by "Atebrin". In the early stages of the war there were doubts in America as to whether the "Atebrin" in use was as effective as that originally produced in Germany. These doubts have since been resolved by thorough clinical and chemical tests. It is an interesting reflection on international relations that it would probably not be possible for us to wage war against the Japanese in the malarious areas of the Pacific if we did not possess an anti-malarial drug introduced by the Germans.

An attempt is being made to stimulate the production of quinine in South America, which was the original source of the drug, but which for some time has had to import supplies for home use from Java. South American trees are of a robust type, but their yield of quinine is not high.

Quinine is a rather unpleasant drug to take and, as described earlier, it is not ideal therapeutically. Numerous attempts are being made to produce a synthetic anti-malarial that will supersede it. Some of the sulphonamides have proved active against experimental malaria, which is produced in animals by plasmodia related to those that

attack human beings. There has been no announcement so far, however, of a new sulphonamide or other drug which can be used successfully against human malaria.

Specific Treatment of Severe Malaria.

The treatment so far outlined is applicable to patients whose attacks are of moderate severity. In the following cases it is necessary that quinine should be given more quickly than is possible when the oral route is used: (*a*) When acute pernicious malaria is present, especially if it takes the form of hyperpyrexia, cerebral malaria, algid malaria or cardiac malaria. (*b*) When an acute pernicious manifestation of malignant tertian malaria may be anticipated because of the combination of the following three findings: more than 5% of the red cells are infected; more than 5% of the infected corpuscles show the multiple ring forms characteristic of malignant tertian malaria; and pigmented asexual forms are present, showing that the parasites are actively developing. (*c*) When the patient cannot swallow, or, because of vomiting, cannot retain orally administered drugs. (*d*) When the disease proves resistant to the routine treatment, resistance being shown by persistence of parasites in the blood, or failure to restore the temperature to normal in three or four days.

When a patient falls into one of the above categories, quinine should be given by the intravenous route, but this method of administration has certain serious dangers and must not be used except in the urgent circumstances already detailed.

If a sterile solution of a quinine salt is not available for injection, such a solution is prepared by dissolving ten grains of the soluble quinine bihydrochloride in ten to twenty cubic centimetres of pyrogen-free water or normal saline solution, and autoclaving the resulting product. It is permissible to repeat this dose after six hours, but a third dose is rarely necessary. The precautions to be observed during the injection are: (*a*) it must be quite certain that the point of the needle is lying free in the lumen of the vein, for any solution that is spilt into the surrounding tissues is liable to cause necrosis; (*b*) the injection should be given very slowly, as the rapid introduction of quinine may cause heart failure.

If it is desired to give quinine intravenously, but the technical difficulty of doing so is too great, intramuscular administration may be used. Some doctors have had unfortunate experiences with this method and have condemned it thoroughly, on account of the liability to thrombosis, massive necrosis, tetanus, gas gangrene, and pyogenic abscesses. This should serve as a warning that at least the utmost care must be taken in maintaining asepsis and in selecting the correct site for injection. The region chosen is the upper and outer quadrant of the *gluteus maximus* muscle; it is dangerous to inject the drug into a blood vessel, or near the sciatic nerve, or near the iliac bone.

A soluble form of "Atebrin" known as "Atebrin Musonate" is also available for intramuscular injection, though it is too toxic for intravenous administration. It does not cause muscle necrosis and is usually considered preferable to quinine for intramuscular use. Whatever rapid method of administration is employed, however, it should be given over in favour of the oral route as soon as the condition of the patient permits.

Detailed Treatment of Acute Pernicious Malaria.

The specific treatment of acute pernicious malaria has already been described: the condition is so urgent that quinine or "Atebrin" has to be given parenterally. In addition, however, non-specific treatment is required.

In malarial hyperpyrexia ordinary sponging is not effective in reducing the temperature and the patient must be stripped, covered with a wet sheet, and vigorously fanned. These measures must be maintained until the rectal temperature falls to 102° F. The patient is then returned to bed and covered with a blanket, and sweating is promoted by the administration of large quantities of alkaline fluid. It is a hopeful sign if sweating breaks out, for this signifies that the patient has available once more the physiological method of reducing temperature.

In cerebral malaria lumbar puncture is indicated if coma persists or if signs of meningeal irritation are prominent. Enough cerebro-spinal fluid is withdrawn to reduce the pressure to normal. Catheterization of the bladder may also be necessary.

Morphine may have to be given in the treatment of malarial dysentery.

Convalescence from Malaria.

The administration of iron to a patient who has had malaria is not necessary as a routine, but if the red cell count is below 4,500,000 per cubic millimetre of blood, or the hæmoglobin value is less than 13·8 grammes per 100 cubic centimetres of blood, iron should be given. If the anæmia is severe, blood transfusion as well as iron is indicated, but the blood has to be from a donor who has not been in the malarial zone.

Suppressive Treatment of Malaria.

No drug is available which is sufficiently active against sporozoites to destroy them without causing toxic effects in the host; and therefore chemotherapy designed to prevent attacks of malaria is suppressive rather than prophylactic. Both quinine and "Atebrin", however, retard the multiplication of asexual parasites, and clinical symptoms do not develop as long as the drug is used. "Atebrin" is now given preference because it is equally effective and more readily available. In hyperendemic regions one tablet of 0·1 gramme is given on six days a week. In areas where the danger from malaria is not too great 0·1 gramme may be given on three alternate days of the week. The skin may be stained yellow by the "Atebrin" and there may be a dry, irritable, scaly thickening of the skin of the palms and soles.

Some results of suppressive treatment with quinine are available from the experience of the Italians in the Abyssinian war. Although half a million troops carried out an extensive campaign in very malarious regions, less than 1% fell victims to the disease and only 23 died from it.[9]

Suppressive treatment of malaria is especially indicated in the case of a wounded soldier, for the trauma and exposure to the weather decrease the man's resistance.

Treatment of Relapses.

A certain number of patients who are treated for malaria are always bound to relapse. Sometimes this is due to omission of the maintenance course, but often it results from the inadequacy of present methods of treatment. The relapse is treated in the first instance by a repetition of the standard course. If relapses continue, a course of organic arsenicals may be tried in the case of benign tertian malaria, "Neosalvarsan" being given once a week in a dose of 0·3 to 0·45 gramme.

Criteria of Cure following Malaria.

In order to check the clinical criteria of cure, thick blood films should be made and examined for parasites on about the third day and the seventeenth day after the completion of the course of treatment.

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